UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,543	09/07/2005	Kazuhiko Imakawa	2005_0329A	5184

513 7590 11/01/2007

WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
KEMMERER, ELIZABETH	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
11/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,543	IMAKAWA ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/3/05; 4/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

Applicant's election with traverse of Group II in the reply filed on 08 August 2007 is acknowledged. The traversal is on the ground(s) that Luster et al. do not anticipate original Group I. This is not found persuasive because all claims to Group I have been canceled, rendering the issue moot.

The requirement is still deemed proper and is therefore made FINAL.

Newly submitted claim 39 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claim 39 is generally directed to a therapeutic method of inhibiting conceptus implantation by administering an IP-10 antibody. The elected invention is generally directed to a therapeutic method of enhancing conceptus implantation by administering and IP-10 protein. The goals of the methods are opposite, and the patient populations do not overlap. Furthermore, the IP-10 antibody and protein have different structures and opposite functions. Therefore, the inventions are independent and distinct.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 39 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Status of Application, Amendments, And/Or Claims

The preliminary amendments of 03 March 2005, 20 April 2005, 07 September 2005, and 08 August 2007 have been entered in full. Claims 1-31 are canceled. Claim 39 is withdrawn from consideration as being directed to a non-elected invention, as explained above. Claims 32-38 are under examination.

Sequence Rules

The instant application is not fully in compliance with the sequence rules, 37 C.F.R. § 1.821-1.825 because each disclosure of a sequence embraced by the definitions set forth in the rules is not accompanied by the required reference to the relevant sequence identifier. This occurs at least in Figures 1 and 2, and pages 69, 87, and 90. Compliance with the sequence rules is required. For sequences appearing in the drawings, reference to the sequence identifiers may be made in the drawings themselves or in the brief description of the drawings.

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "stringent" in claim 32 is a relative term which renders the claim indefinite. The term "stringent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In other words, neither the prior art nor the specification provide an unambiguous definition for the term.

Similarly, the term "essentially equal or equivalent to" in claims 32 and 34 is a relative term which renders the claim indefinite. The term "essentially equal or equivalent to" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Finally, claim 32 recites "thereof" in the last line. It is not clear to what part of the claim "thereof" refers since many different IP-10 structures are listed in the claim.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A) Scope of Enablement:

Claims 32-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of administering mammalian IP-10 protein for therapeutically treating (1) a female subject to promote conceptus

implantation or (2) any subject to chemoattract monocytes or lymphocytes, does not reasonably provide enablement for the methods as broadly claimed, including prophylactic treatment, or administration of IP-10 variants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to methods of treating subjects therapeutically or prophylactically for a variety of purposes. These are to activate conceptus migration, promote conceptus implantation on the uterine wall, reduce sterility, promote pregnancy, control interaction between conceptus and maternal system, activate immunocyte migration, and/or control immune function in the uterus. The claims recite that these goals are achieved by administration of various forms of IP-10 protein to a subject.

The specification discloses a new sequence for ovine IP-10 and provides a sequence alignment between ovine, caprine, human, and mouse IP-10. Experiments to explore the biological activities of ovine IP-10 are also disclosed, and show that IP-10 mRNA and protein levels are increased in ovine and caprine uterus during implantation, interferons induce IP-10 mRNA expression in endometrial explants, IP-10 chemoattracts PBMCs, IP-10 receptor (CXCR3) is expressed in caprine conceptuses, IP-10 binds and is chemotactic for caprine trophoblasts, and IP-10 increases binding of trophoblasts to fibronectin and endometrial cells.

The prior art shows that mammalian IP-10 is chemotactic for activated T cells (Farber, 1997, J. Leuk. Bio. 61:246-257), and monocytes (Taub et al., 1993, J. Exp.

Med. 177:1809-1814). The prior art also discloses that mammalian IP-10 promotes conceptus implantation (US 6013252, paragraph bridging columns 5-6).

However, the scope of patent protection sought by Applicant as defined by the claims is not commensurate with the scope of enabling disclosure set forth in the specification and prior art for the following reasons.

First, regarding the scope of what conditions can be treated with IP-10, the process of the implantation of a conceptus (or embryo) into the uterine wall plays only one small role in the larger concepts of pregnancy, fertility/sterility, interactions between conceptus and maternal systems, immunocyte migration, and immune function in the uterus. For example, treatment of sterility reads on treatment of both male and female subjects for a variety of problems, including failure to ovulate and low sperm count, wherein this variety of problems has no link to conceptus implantation. Similarly, interaction between conceptus and maternal systems involves placental integrity, umbilical cord issues, Rh compatibility, etc., which also have no link to conceptus implantation.

Regarding the scope of IP-10 proteins, neither the specification nor the prior art provide guidance regarding what IP-10 variant proteins retain the desired activity of improving conceptus implantation. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a

reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to determine how to achieve all of the goals set forth in the preamble of the claims with virtually any type of

IP-10-like protein, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

B) New Matter:

Claims 32-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 32-38 read on prophylactic treatment. The specification as originally filed does not appear to have support for this concept. Should Applicant disagree, it would be helpful to point to page and line of the originally filed application for support.

C) Inadequate Written Description:

Claims 32-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. Claims 32 and 34-38 read on administration of a variety of IP-10 proteins and variants. Claim 33 specifically recites IP-10 proteins obtained from human, bovine, buffalo, equine, donkey, ovine, goat, camel, swine, deer, reindeer, yak, canine, cat, and ape. The specification discloses IP-10 sequences from ovine, caprine (goat), human, and mouse sources. As such, these species are representative of the genus of mammalian IP-10 proteins. However, these species are not representative of the genus of artificially generate or non-mammalian IP-10 proteins encompassed by claim 32, for example, nor the particular following species listed in claims 33: bovine, buffalo, equine, donkey, camel, swine, deer, reindeer, yak, canine, cat, and ape.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in claims 32 and 34-38 is a partial structure in the form of a recitation of percent identity or as a function of hybridization. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. In the case of claim 33, there is no written description of the specific sequences of bovine, buffalo, equine, donkey, camel, swine, deer, reindeer, yak, canine, cat, or ape IP-10 protein.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the genus of mammalian IP-10 proteins, or the specific IP-10 proteins from ovine, human, caprine, and mouse, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated mammalian IP-10 proteins or IP-10 proteins comprising the amino acid sequences set forth in Figure 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is

reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 32, 33, and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6013252 (Terao et al., issued 11 January 2000) in view of Luster et al. (1987, Mol. Cell. Biol. 7:3723-3731).

'252 teaches a method of promoting fertilized-ovum implantation, which is simply a different way of saying a method of treating a subject to promote conceptus implantation on the uterine wall. See bottom of column 5. '252 suggests administering

leukocyte chemotactic factors to achieve this goal, and specifically suggests IP-10. See paragraph bridging col. 5-6. This is relevant to claims 32, 36, and 37. '252 suggests that the subject is human at col. 8, lines 15-17, which is pertinent to claim 35. Since '252 teaches methods pertaining to pregnancy and embryo implantation, it implies treatment of female humans, which is pertinent to claim 37. Finally, '252 acknowledges that such treatment is a form of treatment for sterility, or infertility. See col. 8, lines 18-37.

'252 does not teach the structure or source of IP-10.

However, Luster et al. teaches a structure for human IP-10 which meets the structural limitations of claims 32, 33, and 35-38.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to utilize the human IP-10 of Luster et al. in the methods of '252 with a reasonable expectation of success. The motivation to do so is provided by '252 which specifically suggests using IP-10 to promote embryo/conceptus implantation, and the knowledge of those of ordinary skill in the art that it is desirable to treat a human patient with a human protein to decrease the chance of an undesirable immunogenic response.

Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ECK

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646